

10/075,915

=> d his

(FILE 'HOME' ENTERED AT 17:58:57 ON 27 MAR 2002)

FILE 'REGISTRY' ENTERED AT 17:59:05 ON 27 MAR 2002

L1 STRUCTURE UPLOADED  
L2 QUE L1  
L3 33 S L2  
L4 1 S IBOGAMINE/CN  
L5 SCREEN 963 AND 1006  
L6 STRUCTURE UPLOADED  
L7 QUE L6 AND L5  
L8 9 S L7  
L9 115 S L7 SSS FUL

FILE 'CAPLUS' ENTERED AT 18:02:42 ON 27 MAR 2002

L10 405 S L9

FILE 'REGISTRY' ENTERED AT 18:03:56 ON 27 MAR 2002

L11 SCREEN 963 AND 1006  
L12 STRUCTURE UPLOADED  
L13 QUE L12 AND L11  
L14 1 S L13  
L15 25 S L13 FUL SUB=L9

FILE 'CAPLUS' ENTERED AT 18:05:43 ON 27 MAR 2002

L16 285 S L15

FILE 'REGISTRY' ENTERED AT 18:05:55 ON 27 MAR 2002

FILE 'CAPLUS' ENTERED AT 18:06:45 ON 27 MAR 2002

FILE 'REGISTRY' ENTERED AT 18:06:58 ON 27 MAR 2002

FILE 'CAPLUS' ENTERED AT 18:08:30 ON 27 MAR 2002

L17 ANALYZE L16 1- RN : 2640 TERMS

FILE 'REGISTRY' ENTERED AT 18:09:17 ON 27 MAR 2002

L18 1 S 83-74-9/RN  
SET NOTICE 1 DISPLAY  
SET NOTICE LOGIN DISPLAY  
L19 24 S L15 NOT L18

FILE 'CAPLUS' ENTERED AT 18:09:53 ON 27 MAR 2002

L20 58 S L19

FILE 'REGISTRY' ENTERED AT 18:12:04 ON 27 MAR 2002

L21 SCREEN 963 AND 1006  
L22 STRUCTURE UPLOADED  
L23 QUE L22 AND L21  
L24 6 S L23 FUL SUB=L9

FILE 'CAPLUS' ENTERED AT 18:12:43 ON 27 MAR 2002

L25 40 S L24

=> d 17

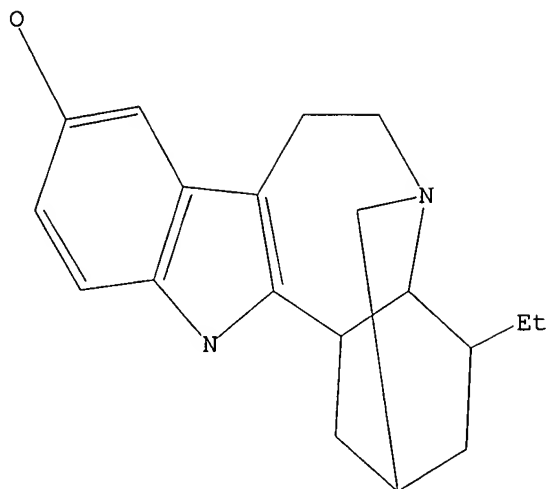
L7 HAS NO ANSWERS

L5 SCR 963 AND 1006

10/075,915

L6

STR



Structure attributes must be viewed using STN Express query preparation.

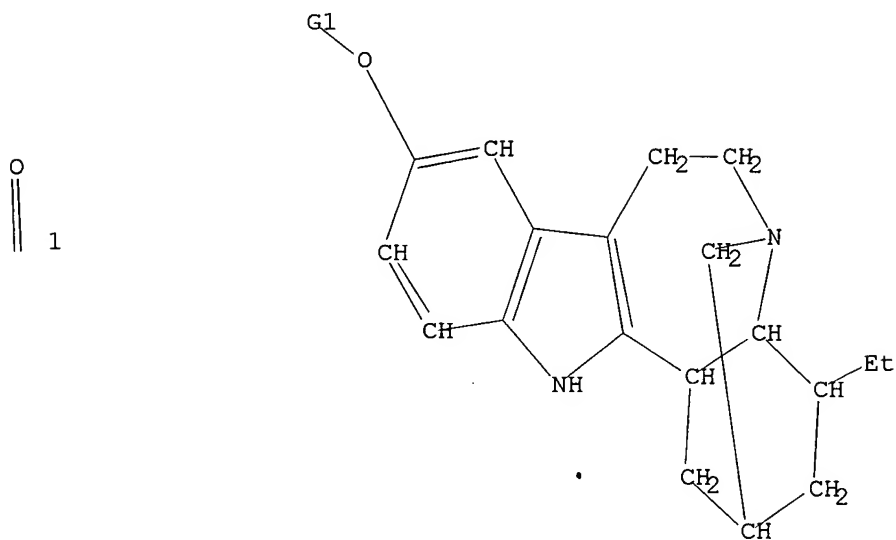
L7 QUE ABB=ON PLU=ON L6 AND L5

=> d 123

L23 HAS NO ANSWERS

L21 SCR 963 AND 1006

L22 STR



G1 H, [01]

Structure attributes must be viewed using STN Express query preparation.

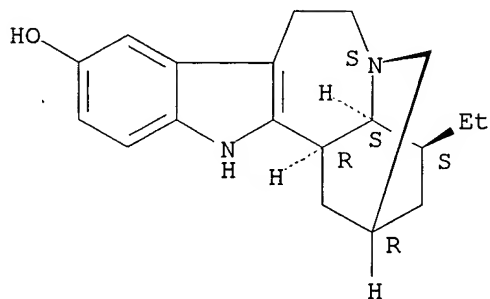
L23 QUE ABB=ON PLU=ON L22 AND L21

10/075,915

=> d bib abs hitstr 125 1-40

L25 ANSWER 1 OF 40 CAPLUS COPYRIGHT 2002 ACS  
 AN 2001:757619 CAPLUS  
 DN 136:111976  
 TI Ibogaine in the treatment of heroin withdrawal  
 AU Mash, Deborah C.; Kovera, Craig A.; Pablo, John; Tyndale, Rachel; Ervin, Frank R.; Kamlet, Jeffrey D.; Hearn, W. Lee  
 CS Departments of Neurology and Pharmacology, University of Miami School of Medicine, Miami, FL, 33124, USA  
 SO Alkaloids (Academic Press) (2001), 56(Ibogaine), 155-171  
 CODEN: ALKAAR; ISSN: 0099-9598  
 PB Academic Press  
 DT Journal; General Review  
 LA English  
 AB A review describes ibogaine treatment as a novel approach to reduce the time it takes to complete the process of detoxification or to further reduce persisting subjective reports of dysphoria and opiate craving. Pharmacol. treatments for heroin addiction currently employ two strategies, i.e., detoxification followed by drug-free abstinence or maintenance treatment with an opioid agonist. Ibogaine treatment has similarities with other detoxification pharmacotherapies, including substitution with a longer-acting opiate, e.g., methadone or buprenorphine. However, ibogaine appears to be a prodrug with the beneficial effects residing in the active metabolite noribogaine. Thus, noribogaine alone is effective in detoxification of heroin-dependent and methadone-maintained patients. (c) 2001 Academic Press.  
 IT **481-88-9**, Noribogaine  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (ibogaine in heroin withdrawal treatment)  
 RN 481-88-9 CAPLUS  
 CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

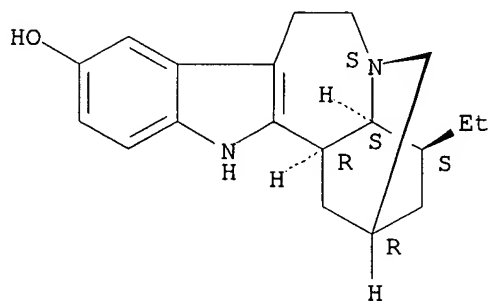
Absolute stereochemistry.



RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 2001:757617 CAPLUS  
DN 136:111974  
TI Comparative neuropharmacology of ibogaine and its O-desmethyl metabolite, noribogaine  
AU Baumann, Michael H.; Pablo, John; Ali, Syed F.; Rothman, Richard B.; Mash, Deborah C.  
CS Clinical Psychopharmacology Section Intramural Research Program National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, 21224, USA  
SO Alkaloids (Academic Press) (2001), 56(Ibogaine), 79-113  
CODEN: ALKAAR; ISSN: 0099-9598  
PB Academic Press  
DT Journal; General Review  
LA English  
AB A review, on the comparative neurobiol. of ibogaine and noribogaine in rodent species. The data presented showed that ibogaine interacts with multiple neurotransmitter systems known to modulate drug addiction. The in vitro pharmacol. activity of ibogaine is further complicated by the metabolic conversion of ibogaine to its active O-desmethyl metabolite, noribogaine, in rats, monkeys, and humans. Noribogaine might contribute to the antiaddictive properties of systematically administered ibogaine. It might also be the active compd. mediating the long-term actions of ibogaine. (c) 2001 Academic Press.  
IT **481-88-9, Noribogaine**  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(comparative neuropharmacol. of ibogaine and its O-desmethyl metabolite, noribogaine)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

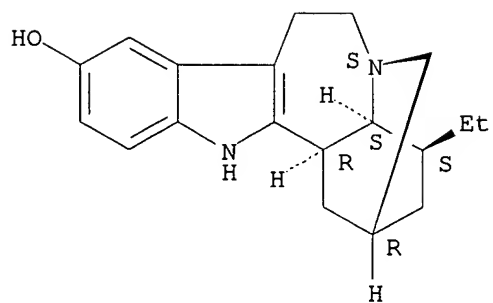


RE.CNT 152 THERE ARE 152 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 2001:321619 CAPLUS  
DN 135:132300  
TI In vivo neurobiological effects of ibogaine and its O-desmethyl  
metabolite, 12-hydroxyibogamine (noribogaine), in rats  
AU Baumann, Michael H.; Rothman, Richard B.; Pablo, John P.; Mash, Deborah C.  
CS Clinical Psychopharmacology Section, Intramural Research Program, National  
Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA  
SO Journal of Pharmacology and Experimental Therapeutics (2001), 297(2),  
531-539  
CODEN: JPETAB; ISSN: 0022-3565  
PB American Society for Pharmacology and Experimental Therapeutics  
DT Journal  
LA English  
AB Ibogaine is a naturally occurring compd. with purported antiaddictive  
properties. When administered to primates, ibogaine is rapidly  
o-demethylated to form the metabolite 12-hydroxyibogamine (noribogaine).  
Peak blood levels of noribogaine exceed those of ibogaine, and noribogaine  
persists in the bloodstream for at least 1 day. Very few studies have  
systematically evaluated the neurobiol. effects of noribogaine in vivo.  
In the present series of expts., we compared the effects of i.v.  
administration of ibogaine and noribogaine (1 and 10 mg/kg) on motor  
behaviors, stress hormones, and extracellular levels of dopamine (DA) and  
serotonin (5-HT) in the nucleus accumbens of male rats. Ibogaine caused  
dose-related increases in tremors, whereas noribogaine did not. Both  
ibogaine and noribogaine produced significant elevations in plasma  
corticosterone and prolactin, but ibogaine was a more potent stimulator of  
corticosterone secretion. Neither drug altered extracellular DA levels in  
the nucleus accumbens. However, both drugs increased extracellular 5-HT  
levels, and noribogaine was more potent in this respect. Results from in  
vitro expts. indicated that ibogaine and noribogaine interact with 5-HT  
transporters to inhibit 5-HT uptake. The present findings demonstrate  
that noribogaine is biol. active and undoubtedly contributes to the in  
vivo pharmacol. profile of ibogaine in rats. Noribogaine is approx. 10  
times more potent than ibogaine as an indirect 5-HT agonist. More  
importantly, noribogaine appears less apt to produce the adverse effects  
assocd. with ibogaine, indicating the metabolite may be a safer  
alternative for medication development.  
IT 481-88-9, Noribogaine  
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(in vivo neurobiol. effects of ibogaine and its O-desmethyl metabolite,  
12-hydroxyibogamine (noribogaine), in rats)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915

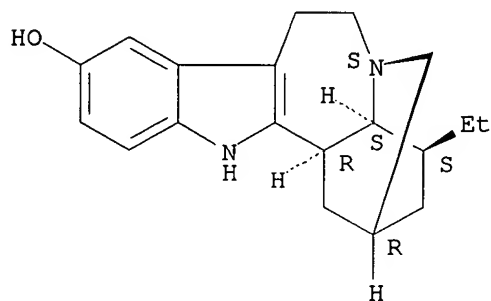


RE.CNT 43      THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/075,915

L25 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 2001:264421 CAPLUS  
DN 135:40900  
TI Noribogaine: an active metabolite of the indole alkaloid ibogaine as an  
anti-addiction pharmacotherapy  
AU Pablo, John P.  
CS Univ. of Miami, Coral Gables, FL, USA  
SO (2000) 140 pp. Avail.: UMI, Order No. DA9972552  
From: Diss. Abstr. Int., B 2000, 61(5), 2409  
DT Dissertation  
LA English  
AB Unavailable  
IT **481-88-9**, Noribogaine  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
(Biological study); PROC (Process)  
(ibogaine indole alkaloid metabolite noribogaine as anti-addiction  
pharmacotherapy)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

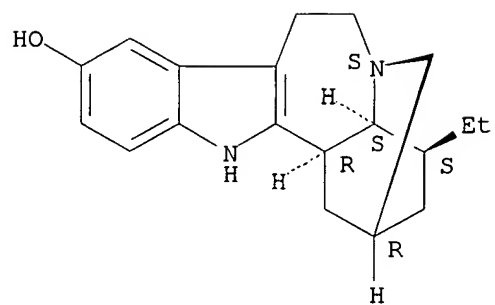




L25 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 2000:842753 CAPLUS  
DN 134:360947  
TI Ibogaine: Complex pharmacokinetics, concerns for safety, and preliminary efficacy measures  
AU Mash, Deborah C.; Kovera, Craig A.; Pablo, John; Tyndale, Rachel F.; Ervin, Frank D.; Williams, Izben C.; Singleton, Edward G.; Mayor, Manny  
CS Department of Neurology, University of Miami School of Medicine, Miami, FL, 33136, USA  
SO Annals of the New York Academy of Sciences (2000), 914 (Neurobiological Mechanisms of Drugs of Abuse), 394-401  
CODEN: ANYAA9; ISSN: 0077-8923  
PB New York Academy of Sciences  
DT Journal  
LA English  
AB Ibogaine is an indole alkaloid found in the roots of Tabernanthe Iboga (Apocynaceae family), a rain forest shrub that is native to western Africa. Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger, and thirst, and in higher doses as a sacrament in religious rituals. Members of American and European addict self-help groups have claimed that ibogaine promotes long-term drug abstinence from addictive substances, including psychostimulants, and opiates. Anecdotal reports attest that a single dose of ibogaine eliminates opiate withdrawal symptoms and reduces drug craving for extended periods of time. The purported efficacy of ibogaine for the treatment of drug dependence may be due in part to an active metabolite. The majority of ibogaine biotransformation proceeds via CYP2D6, including the O-demethylation of ibogaine to 12-hydroxyibogamine (noribogaine). Blood concn.-time effect profiles of ibogaine and noribogaine obtained for individual subjects after single oral dose administrations demonstrate complex pharmacokinetic profiles. Ibogaine has shown preliminary efficacy for opiate detoxification and for short-term stabilization of drug-dependent persons as they prep. to enter substance abuse treatment. The authors report here that ibogaine decreased craving for cocaine and heroin during inpatient detoxification. Self-reports of depressive symptoms were also lower after ibogaine treatment and at 30 days after program discharge. Because ibogaine is cleared rapidly from the blood, the beneficial aftereffects of the drug on craving and depressed mood may be related to the effects of noribogaine on the central nervous system.  
IT 481-88-9, Noribogaine  
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)  
(anti-addictive agent ibogaine)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 2000:842750 CAPLUS

DN 134:361267

TI Noribogaine (12-hydroxyibogamine): A biologically active metabolite of the antiaddictive drug ibogaine

AU Baumann, M. H.; Pablo, J. P.; Ali, S. F.; Rothman, R. B.; Mash, D. C.

CS Clinical Psychopharmacology Section, Intramural Research Program, NIDA, NIH, Baltimore, MD, 21224, USA

SO Annals of the New York Academy of Sciences (2000), 914 (Neurobiological Mechanisms of Drugs of Abuse), 354-368

CODEN: ANYAA9; ISSN: 0077-8923

PB New York Academy of Sciences

DT Journal

LA English

AB Ibogaine (IBO) is a plant-derived alkaloid that is being evaluated as a possible medication for substance use disorders. When administered peripherally to monkeys and humans, IBO is rapidly converted to an o-demethylated metabolite, 12-hydroxyibogamine (NORIBO). We have found in rats that peak blood levels of NORIBO can exceed those of the parent compd., and NORIBO persists in the bloodstream for at least 24 h. Surprisingly few studies have examd. the in vivo biol. activity of NORIBO. In the present series of expts., we compared the effects of i.v. administration of IBO and NORIBO (1 and 10 mg/kg) on unconditioned behaviors, circulating stress hormones, and extracellular levels of dopamine (DA) and serotonin (5-HT) in the nucleus accumbens of male rats. IBO caused dose-related increases in tremors and forepaw treading, whereas NORIBO did not. Both IBO and NORIBO produced significant elevations in plasma corticosterone and prolactin, but IBO was more potent as a stimulator of corticosterone secretion. Neither drug affected extracellular DA levels in the nucleus accumbens. However, both IBO and NORIBO increased extracellular 5-HT levels, and NORIBO was more potent in this regard. The present data demonstrate that NORIBO is biol. active and undoubtedly contributes to the in vivo pharmacol. profile of IBO in rats. Most importantly, NORIBO appears less likely to produce the adverse effects assocd. with IBO (i.e., tremors and stress-axis activation), suggesting that the metabolite may be a safer alternative for medication development.

IT 481-88-9, Noribogaine

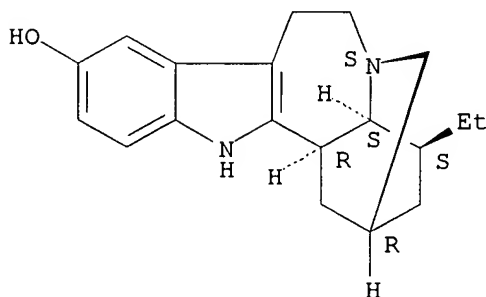
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)

(noribogaine: a biol. active metabolite of antiaddictive drug ibogaine)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



10/075,915

RE.CNT 40      THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 2000:716746 CAPLUS

DN 134:231357

TI Ibogaine and noribogaine: comparing parent compound to metabolite

AU Zubaran, Carlos

CS Department of Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

SO CNS Drug Reviews (2000), 6(3), 219-240

CODEN: CDREFB; ISSN: 1080-563X

PB Neva Press

DT Journal; General Review

LA English

AB A review with 112 refs. Ibogaine is one of the psychoactive alkaloids found in the West African shrub *Tabernanthe iboga*. Since the 1980s, a series of US patents have claimed efficacy for ibogaine in the treatment of drug addiction. Since then, >60 scientific publications on ibogaine and drug addiction have been published. Ibogaine has an acute and a prolonged effect on neurochem. and behavior. Its metabolite, noribogaine (12-hydroxyibogamine), is produced through metabolic demethylation soon after oral ibogaine administration. Although they share similar chem. structures, ibogaine and noribogaine display different binding profiles. In rodents, both ibogaine and noribogaine decreased morphine and cocaine intake and modulated dopaminergic transmission. In rats trained to discriminate ibogaine from saline, complete generalization to noribogaine was obtained. Attempts to correlate brain levels of both the parent compd. and the metabolite indicate that noribogaine is primarily responsible for ibogaine's discriminative-stimulus effects. Ibogaine-induced neurotoxicity tends to occur at doses much higher than the proposed dose for humans, but caution is important when extrapolating data from ibogaine's effects in rodents. Although a definitive clin. validation of purported ibogaine effects is still unavailable, ibogaine has opened new perspectives in the investigation of pharmacotherapies for drug addiction.

IT 481-88-9, Noribogaine

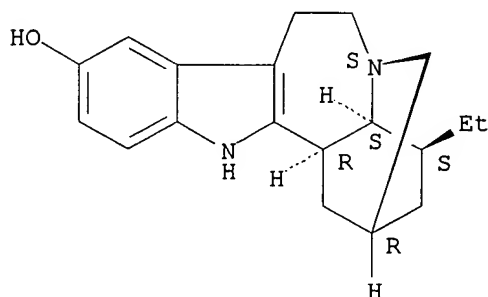
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)

(pharmacol. of ibogaine and its metabolite noribogaine with respect to treatment of drug addiction)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



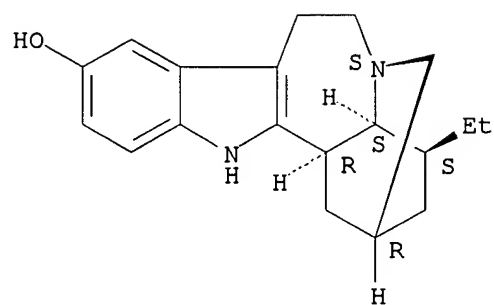
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RE.CNT 112 THERE ARE 112 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 2000:547065 CAPLUS  
DN 134:405  
TI Development of novel medications for drug addiction. The legacy of an African shrub  
AU Glick, Stanley D.; Maisonneuve, Isabelle M.  
CS Department of Pharmacology and Neuroscience, Albany Medical College, Albany, NY, 12208, USA  
SO Annals of the New York Academy of Sciences (2000), 909 (New Medications for Drug Abuse), 88-103  
CODEN: ANYAA9; ISSN: 0077-8923  
PB New York Academy of Sciences  
DT Journal  
LA English  
AB Ibogaine, one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga*, has been claimed to be effective in treating multiple forms of drug abuse. Problems assocd. with side effects of ibogaine have spawned a search for more effective and safer structural derivs. 18-Methoxycoronaridine (18-MC), a novel iboga alkaloid congener, appears to have substantial potential for broad use as an antiaddictive therapy. Like ibogaine (40 mg/kg), 18-MC (40 mg/kg) decreased the i.v. self-administration of morphine and cocaine and the oral self-administration of EtOH and nicotine in rats; unlike ibogaine, 18-MC did not affect responding for a nondrug reinforcer (water). Ibogaine and 18-MC appear to reduce the reinforcing efficacies, rather than the potencies, of drugs of abuse. Both ibogaine and 18-MC decreased extracellular levels of dopamine in the rat nucleus accumbens, while only ibogaine increased serotonin levels in this brain region. Both ibogaine and 18-MC blocked morphine-induced and nicotine-induced dopamine release in the accumbens; only ibogaine enhanced cocaine-induced increases in dopamine. Ibogaine produced whole-body tremors and, at high doses ( $>100$  mg/kg), cerebellar damage; 18-MC did not produce these effects. Ibogaine, but not 18-MC, caused bradycardia at high doses. Ibogaine and its metabolite noribogaine had low- $\mu$ M affinities for  $\kappa$  and  $\mu$  opioid receptors, NMDA receptors, 5HT<sub>3</sub> receptors,  $\sigma$ -2 sites, sodium channels and the serotonin transporter. 18-MC had low- $\mu$ M affinities at all three opioid receptors and at 5HT<sub>3</sub> receptors but much lower or no affinities for NMDA and  $\sigma$ -2 receptors, sodium channels, and the serotonin transporter. Both 18-MC and ibogaine were sequestered in fat; like ibogaine, 18-MC probably has an active metabolite. 18-MC also has (+) and (-) enantiomers, both of which are active. The data indicate that 18-MC should be safer than ibogaine and at least as effective as an antiaddictive drug.  
IT **481-88-9**, Noribogaine  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(ibogaine, noribogaine and methoxycoronaridine binding to brain receptors)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915



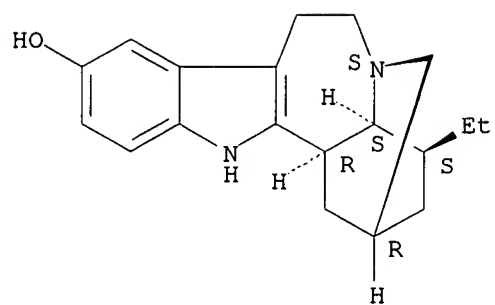
RE.CNT 55      THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L25 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 2000:171768 CAPLUS  
DN 132:318283  
TI Modulation of cellular calcium by sigma-2 receptors: release from  
intracellular stores in human SK-N-SH neuroblastoma cells  
AU Vilner, Bertold J.; Bowen, Wayne D.  
CS Unit on Receptor Biochemistry and Pharmacology, Laboratory of Medicinal  
Chemistry, National Institute of Diabetes and Digestive and Kidney  
Diseases, National Institutes of Health, Bethesda, MD, USA  
SO J. Pharmacol. Exp. Ther. (2000), 292(3), 900-911  
CODEN: JPETAB; ISSN: 0022-3565  
PB American Society for Pharmacology and Experimental Therapeutics  
DT Journal  
LA English  
AB Human SK-N-SH neuroblastoma cells expressed sigma-1 and sigma-2 receptors  
with similar pharmacol. profiles to those of rodent-derived tissues,  
although sigma-2 receptors exhibited some affinity differences that might  
suggest heterogeneity or species differences. Structurally diverse sigma  
ligands produced two types of increases in intracellular (cytosolic) Ca<sup>2+</sup>  
concn. ([Ca<sup>2+</sup>]<sub>i</sub>) in these cells. CB-64D, CB-64L, JL-II-147, BD737, LR172,  
BD1008, haloperidol, reduced haloperidol, and ibogaine all produced an  
immediate, dose-dependent, and transient rise in [Ca<sup>2+</sup>]<sub>i</sub>. Sigma-inactive  
comps. structurally similar to the most active sigma ligands and ligands  
for several neurotransmitter receptors produced little or no effect. The  
high activity of CB-64D and ibogaine (sigma-2-selective ligands) compared  
with the low activity of (+)-pentazocine and other (+)-benzomorphans  
(sigma-1-selective ligands), in addn. to enantioselectivity for CB-64D  
over CB-64L, strongly indicated mediation by sigma-2 receptors. The  
effect of CB-64D and BD737 was blocked by the sigma antagonists BD1047 and  
BD1063, further confirming specificity as a receptor-mediated event. The  
transient rise in [Ca<sup>2+</sup>]<sub>i</sub> occurred in the absence of extracellular Ca<sup>2+</sup>  
and was completely eliminated by pretreatment of cells with thapsigargin.  
Thus, sigma-2 receptors stimulate a transient release of Ca<sup>2+</sup> from the  
endoplasmic reticulum. Prolonged exposure of cells to sigma-receptor  
ligands resulted in a latent and sustained rise in [Ca<sup>2+</sup>]<sub>i</sub>, with a  
pharmacol. profile identical to that of the transient rise. This  
sustained rise in [Ca<sup>2+</sup>]<sub>i</sub> was affected by neither the removal of  
extracellular Ca<sup>2+</sup> nor thapsigargin pretreatment, suggesting latent  
sigma-2 receptor-induced release from thapsigargin-insensitive  
intracellular Ca<sup>2+</sup> stores. Sigma-2 receptors may use Ca<sup>2+</sup> signals in  
producing cellular effects.  
IT 481-88-9, Noribogaine  
RL: BAC (Biological activity or effector, except adverse); BUU (Biological  
use, unclassified); BIOL (Biological study); USES (Uses)  
(modulation of cellular calcium by .sigma.-2 receptors: release from  
intracellular stores in human SK-N-SH neuroblastoma cells)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

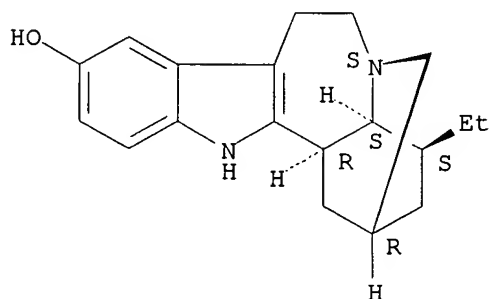
Absolute stereochemistry.

10/075,915



L25 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2002 ACS  
 AN 1999:430105 CAPLUS  
 DN 131:252403  
 TI Noribogaine generalization to the ibogaine stimulus: correlation with  
 noribogaine concentration in rat brain  
 AU Zubaran, C.; Shoaid, M.; Stolerman, I. P.; Pablo, J.; Mash, D. C.  
 CS Section of Behavioural Pharmacology, Institute of Psychiatry, London, SE5  
 8AF, UK  
 SO Neuropsychopharmacology (1999), 21(1), 119-126  
 CODEN: NEROEW; ISSN: 0893-133X  
 PB Elsevier Science Inc.  
 DT Journal  
 LA English  
 AB The discriminative stimulus effects of ibogaine and noribogaine in rats  
 have been examd. in relation to their concns. in blood plasma and brain  
 regions and to receptor systems through which they have been proposed to  
 act. Rats were trained to discriminate ibogaine (10 mg/kg IP), the NMDA  
 antagonist dizocilpine (0.08 mg/kg IP) or the .kappa.-opioid agonist  
 U50,488 (5 mg/kg IP) from vehicle in a std. two-lever operant conditioning  
 procedure with a tandem VI-FR schedule of food reinforcement. Only rats  
 trained on ibogaine generalized to noribogaine, which was approx. twice as  
 potent as the parent compd. Noribogaine was detected in plasma and brain  
 after administration of ibogaine and noribogaine. At the ED50 doses for  
 the discriminative effect, the estd. concns. of noribogaine in plasma,  
 cerebral cortex, and striatum were similar regardless of whether ibogaine  
 or noribogaine was administered. The findings suggest that the metabolite  
 noribogaine may be devoid of NMDA antagonist and .kappa.-opioid agonist  
 discriminative effects and that it may play a major role in mediating the  
 discriminative stimulus effect of ibogaine.  
 IT **481-88-9**, Noribogaine  
 RL: BAC (Biological activity or effector, except adverse); BIOL  
 (Biological study)  
 (noribogaine generalization to ibogaine stimulus and correlation with  
 noribogaine concn. in rat brain)  
 RN 481-88-9 CAPLUS  
 CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1999:184122 CAPLUS

DN 130:205166

TI Noribogaine in the treatment of pain and drug addiction

IN Mash, Deborah C.

PA Novoneuron, Inc., USA

SO PCT Int. Appl., 16 pp.

CODEN: PIXXD2

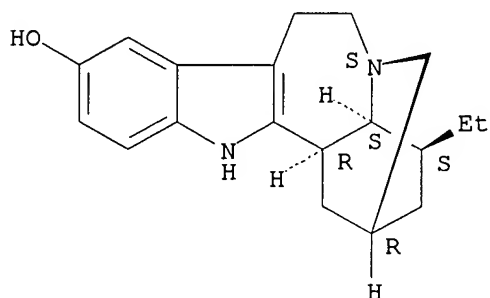
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9911250	A2	19990311	WO 1998-US18284	19980903
	WO 9911250	A3	19990805		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9892174	A1	19990322	AU 1998-92174	19980903
	EP 1009407	A2	20000621	EP 1998-944698	19980903
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
PRAI	US 1997-57921P	P	19970904		
	WO 1998-US18284	W	19980903		
AB	The present invention is directed to methods of treating patients for pain by administering noribogaine. Noribogaine may also be used to treat patients for the symptoms assocd. with withdrawal from drug dependency. In the latter case, the noribogaine treatment should be supplemented with the administration of an opioid antagonist such as naloxone.				
IT	<b>481-88-9</b> , Noribogaine				
	RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (noribogaine and opioid antagonists for treatment of pain and drug addiction)				
RN	481-88-9 CAPLUS				
CN	Ibogamin-12-ol (9CI) (CA INDEX NAME)				

Absolute stereochemistry.



L25 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1998:656503 CAPLUS

DN 129:270563

TI Enhancement of morphine antinociception by ibogaine and noribogaine in morphine-tolerant mice

AU Sharma, Shyam Sunder; Bhargava, Hemendra N.

CS Department Pharmaceutics Pharmacodynamics (M/C 865), Health Sciences Center, University Illinois, Chicago, IL, 60612, USA

SO Pharmacology (1998), 57(5), 229-232

CODEN: PHMGBN; ISSN: 0031-7012

PB S. Karger AG

DT Journal

LA English

AB The effects of ibogaine, an alkaloid isolated from the bark of the African shrub, *Tabernaemontana iboga*, and noribogaine, a metabolite of ibogaine, on morphine antinociception were detd. in male Swiss-Webster mice. Mice were rendered tolerant to morphine by implanting them with a pellet contg. 25 mg of morphine base for 3 days. Placebo pellet-implanted mice served as controls. The antinociception of morphine (10 mg/kg, s.c.) was detd. alone or in combination with an appropriate dose of ibogaine or noribogaine. Tolerance to morphine developed as a result of morphine pellet implantation as evidenced by decreased antinociceptive response to morphine. Both ibogaine and noribogaine dose-dependently enhanced morphine antinociception in morphine-tolerant but not in morphine-naive mice. It is concluded that ibogaine and noribogaine enhance morphine antinociception in morphine-tolerant mice.

IT 481-88-9, Noribogaine

RL: BAC (Biological activity or effector, except adverse); THU

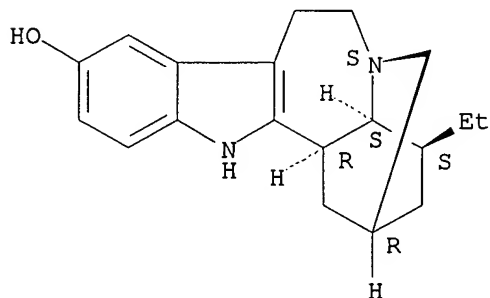
(Therapeutic use); BIOL (Biological study); USES (Uses)

(enhancement of morphine antinociception by ibogaine and noribogaine in morphine-tolerant mice)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

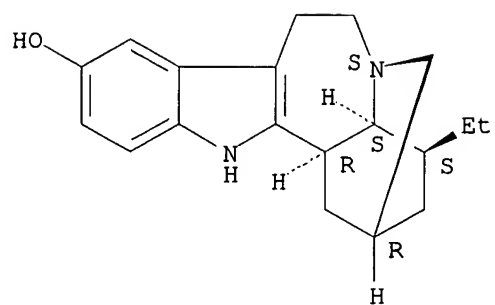
Absolute stereochemistry.



L25 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1998:540906 CAPLUS  
DN 129:225279  
TI Cytochrome P 450 2D6 catalyzes the O-demethylation of the psychoactive alkaloid ibogaine to 12-hydroxyibogamine  
AU Obach, R. Scott; Pablo, John; Mash, Deborah C.  
CS Central Research Division, Department of Drug Metabolism, Groton, CT, 06340, USA  
SO Drug Metab. Dispos. (1998), 26(8), 764-768  
CODEN: DMDSAI; ISSN: 0090-9556  
PB Williams & Wilkins  
DT Journal  
LA English  
AB Ibogaine is a psychoactive alkaloid that possesses potential as an agent to treat opiate and cocaine addiction. The primary metabolite arises via O-demethylation at the 12-position to yield 12-hydroxyibogamine. Evidence is presented that the O-demethylation of ibogaine obsd. in human hepatic microsomes is catalyzed primarily by the polymorphically expressed cytochrome P 450 2D6 (CYP2D6). An enzyme kinetic examn. of ibogaine O-demethylase activity in pooled human liver microsomes suggested that 2 (or more) enzymes are involved in this reaction: one with a low  $K_{Mapp}$  (1.1  $\mu M$ ) and the other with a high  $K_{Mapp}$  ( $>200 \mu M$ ). The low  $K_{Mapp}$  activity comprised  $>95\%$  of total intrinsic clearance. Human liver microsomes from 3 individual donors demonstrated similar enzyme kinetic parameters (mean  $K_{Mapp} = 0.55 \pm 0.09 \mu M$  and  $310 \pm 10 \mu M$  for low and high  $K_M$  activities, resp.). However, a 4th human microsome sample that appeared to be a phenotypic CYP2D6 poor metabolizer possessed only the high  $K_{Mapp}$  activity. In hepatic microsomes from a panel of human donors, the low  $K_{Mapp}$  ibogaine O-demethylase activity correlated with CYP2D6-catalyzed bufuralol 1'-hydroxylase activity but not with other P 450 isoform-specific activities. Quinidine, a CYP2D6-specific inhibitor, inhibited ibogaine O-demethylase ( $IC_{50} = 0.2 \mu M$ ), whereas other P 450 isoform-specific inhibitors did not inhibit this activity. Also, of a battery of recombinant heterologously expressed human P 450 isoforms, only rCYP2D6 possessed significant ibogaine O-demethylase activity. Thus, it is concluded that ibogaine O-demethylase is catalyzed by CYP2D6 and that this isoform is the predominant enzyme of ibogaine O-demethylation in humans. The potential pharmacol. implications of these findings are discussed.  
IT 481-88-9, 12-Hydroxyibogamine  
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(O-demethylation of psychoactive alkaloid ibogaine to 12-hydroxyibogamine catalyzed by cytochrome P 4502D6)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915



L25 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1998:469623 CAPLUS

DN 129:170461

TI Medication development of ibogaine as a pharmacotherapy for drug dependence

AU Mash, Deborah C.; Kovera, Craig A.; Buck, Billy E.; Norenberg, Michael D.; Shapshak, Paul; Hearn, W. Lee; Sanchez-Ramos, Juan

CS Departments of Neurology, Psychiatry, Orthopedics, and Pathology, University of Miami School of Medicine, Miami, FL, 33136, USA

SO Ann. N. Y. Acad. Sci. (1998), 844 (Neurochemistry of Drugs of Abuse), 274-292

CODEN: ANYAA9; ISSN: 0077-8923

PB New York Academy of Sciences

DT Journal; General Review

LA English

AB The potential for deriving new psychotherapeutic medications from natural sources has led to renewed interest in rain forest plants as a source of lead compds. for the development of antiaddiction medications. Ibogaine is an indole alkaloid found in the roots of *Tabernanthe iboga*. Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger, and in higher doses as a sacrament in religious rituals. Members of American and European addict self-help groups have claimed that ibogaine promotes long-term drug abstinence from addictive substances, including psychostimulants and cocaine. Anecdotal reports attest that a single dose of ibogaine eliminates withdrawal symptoms and reduces drug cravings for extended periods of time. The purported antiaddictive properties of ibogaine require rigorous validation in humans. We have initiated a rising tolerance study using single administration to assess the safety of ibogaine for the treatment of cocaine dependency. The primary objectives of the study are to det. safety, pharmacokinetics and dose effects, and to identify relevant parameters of efficacy in cocaine-dependent patients. Pharmacokinetic and pharmacodynamic characteristics of ibogaine in humans are assessed by analyzing the concn.-time data of ibogaine and its desmethyl metabolite (noribogaine) from the phase I trial, and by conducting in vitro expts. to elucidate the specific disposition processes involved in the metab. of both parent drug and metabolite. A review of ibogaine use and effects is added.

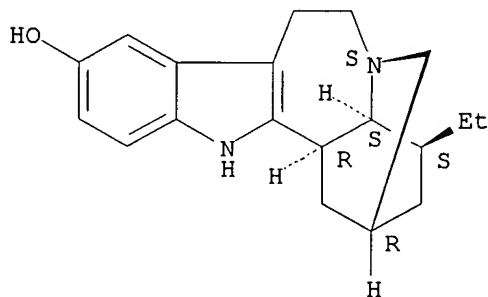
IT 481-88-9, Noribogaine

RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative) (ibogaine, pharmacokinetics and use in the pharmacotherapy for drug dependence)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

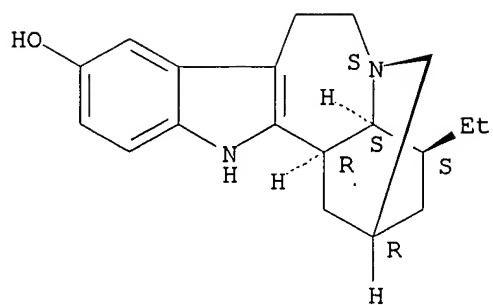




L25 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1998:469618 CAPLUS  
DN 129:239769  
TI Mechanisms of antiaddictive actions of ibogaine  
AU Glick, Stanley D.; Maisonneuve, Isabelle M.  
CS Department of Pharmacology and Neuroscience, A-136, Albany Medical  
College, Albany, NY, 12208, USA  
SO Ann. N. Y. Acad. Sci. (1998), 844 (Neurochemistry of Drugs of Abuse),  
214-226  
CODEN: ANYAA9; ISSN: 0077-8923  
PB New York Academy of Sciences  
DT Journal  
LA English  
AB Ibogaine, an alkaloid extd. from Tabernanthe iboga, is being studied as a  
potential long-acting treatment for opioid and stimulant abuse as well as  
for alcoholism and smoking. Studies in this lab. have used animal models  
to characterize ibogaine's interactions with drugs of abuse, and to  
investigate the mechanisms responsible. Ibogaine, as well as its  
metabolite, noribogaine, can decrease both morphine and cocaine  
self-administration for several days in some rats; shorter-lasting effects  
appear to occur on ethanol and nicotine intake. Acutely, both ibogaine  
and noribogaine decrease extra-cellular levels of dopamine in the nucleus  
accumbens of the rat brain. Ibogaine pretreatment (19 h beforehand)  
blocks morphine-induced dopamine release and morphine-induced locomotor  
hyperactivity while, in contrast, it enhances similar effects of  
stimulants (cocaine and amphetamine). Ibogaine pretreatment also blocks  
nicotine-induced dopamine release. Both ibogaine and noribogaine bind to  
kappa opioid and N-methyl-D-aspartate (NMDA) receptors and to serotonin  
uptake sites; ibogaine also binds to sigma-2 and nicotinic receptors. The  
relative contributions of these actions are being assessed. Our ongoing  
studies in rats suggest that kappa agonist and NMDA antagonist actions  
contribute to ibogaine's effects on opioid and stimulant  
self-administration, while the serotonergic actions may be more important  
for ibogaine-induced decreases in alc. intake. A nicotinic antagonist  
action may mediate ibogaine-induced redn. of nicotine preferences in rats.  
A sigma-2 action of ibogaine appears to mediate its neurotoxicity. Some  
effects of ibogaine (e.g., on morphine and cocaine self-administration,  
morphine-induced hyperactivity, cocaine-induced increases in nucleus  
accumbens dopamine) are mimicked by a kappa agonist (U50,488) and/or a  
NMDA antagonist (MK-801). Moreover, a combination of a kappa antagonist  
and a NMDA agonist will partially reverse several of ibogaine's effects.  
Ibogaine's long-term effects may be mediated by slow release from fat  
tissue (where ibogaine is sequestered) and conversion to noribogaine.  
Different receptors, or combinations of receptors, may mediate  
interactions of ibogaine with different drugs of abuse.  
IT **481-88-9, Noribogaine**  
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic  
formation); THU (Therapeutic use); BIOL (Biological study); FORM  
(Formation, nonpreparative); USES (Uses)  
(mechanisms of antiaddictive actions of ibogaine)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915



L25 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1998:466864 CAPLUS

DN 129:211558

TI Acute iboga alkaloid effects on extracellular serotonin (5-HT) levels in nucleus accumbens and striatum in rats

AU Wei, D.; Maisonneuve, I. M.; Kuehne, M. E.; Glick, S. D.

CS Department of Pathology and Laboratory Medicine, Albany Medical College, Albany, NY, 12208, USA

SO Brain Res. (1998), 800(2), 260-268

CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier Science B.V.

DT Journal

LA English

AB The iboga alkaloid, ibogaine, its metabolite, noribogaine, and the congener, 18-methoxycoronaridine (18-MC) have all been claimed to have anti-addictive properties in animal models, but the mechanisms underlying these effects are unclear. Ibogaine and noribogaine were shown to have affinity for the serotonin transporter, and inhibition of serotonin reuptake has been proposed to be involved in their anti-addictive actions. It is not known yet if 18-MC also has this property. In vivo microdialysis and HPLC (microbore) were used to det. acute changes in extracellular serotonin levels in nucleus accumbens (NAC) and striatum (STR) after both i.p. (40 mg/kg for all drugs) and i.v. (1-10 mg/kg for ibogaine and noribogaine) drug administration in awake freely moving female Sprague-Dawley rats (250-275 g). After i.p. administration, ibogaine, noribogaine and 18-MC had very different effects on extracellular serotonin levels in both NAC and STR: ibogaine elicited large increases (up to 25-fold in NAC and 10-fold in STR), noribogaine produced moderate increases (up to 8-fold in NAC and 5-fold in STR), and 18-MC had no effect in either brain region. These and other data suggest that (1) the serotonergic system may not be an essential factor in the anti-addictive actions of these drugs; (2) ibogaine (or an unidentified metabolite) may release serotonin as well as inhibit its reuptake; (3) stimulation of the ascending serotonergic system may mediate ibogaine's hallucinogenic effect; and (4) 18-MC probably has no affinity for the serotonin transporter, and is unlikely to be a hallucinogen.

IT 481-88-9, Noribogaine

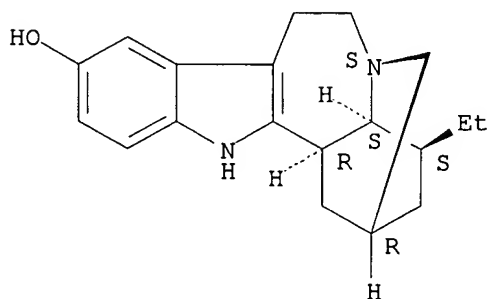
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(iboga alkaloid effects on extracellular serotonin in nucleus accumbens and striatum in rats)

RN 481-88-9 CAPLUS

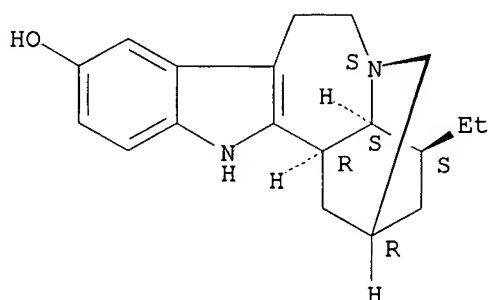
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1998:108539 CAPLUS  
DN 128:200970  
TI Noribogaine stimulates naloxone-sensitive [35S]GTP.gamma.S binding  
AU Pablo, John P.; Mash, Deborah C.  
CS Departments of Neurology (D4-5) and Molecular and Cellular Pharmacology,  
University of Miami School of Medicine, Miami, FL, USA  
SO NeuroReport (1998), 9(1), 109-114  
CODEN: NERPEZ; ISSN: 0959-4965  
PB Rapid Science Publishers  
DT Journal  
LA English  
AB Noribogaine is formed in vivo by the O-demethylation of the indole  
alkaloid ibogaine. We report here that noribogaine acts as a full agonist  
at the .mu.-opioid receptor. Noribogaine-stimulated guanylyl  
5'.gamma.-[35S]thio-triphosphate ([35S]GTP.gamma.S) was studied in rat  
thalamic membranes to measure activation of guanine nucleotide binding  
proteins (G-proteins) in the presence of excess GDP. Noribogaine caused a  
170% increase above basal [35S]GTP.gamma.S binding at sub-micromolar  
effective concns. (EC50) in a naloxone-sensitive manner, confirming that  
this effect was an opioid receptor-mediated process. The level of  
intrinsic activity for noribogaine in these assays was comparable to the  
full agonists DAMGO and morphine. In contrast, ibogaine had no  
significant effect on [35S]GTP.gamma.S binding over a similar concn.  
range. The efficacy of noribogaine as a full .mu.-opioid agonist may  
explain ibogaine's ability to block the acute signs of opiate withdrawal  
and its suppressive effects on morphine self-administration.  
IT **481-88-9**, Noribogaine  
RL: BAC (Biological activity or effector, except adverse); BIOL  
(Biological study)  
(noribogaine stimulates naloxone-sensitive GTP.gamma.S binding to G  
proteins in relation to opioid receptors)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1998:64806 CAPLUS

DN 128:213189

TI Behavioral and biochemical evidence for a nonessential 5-HT<sub>2A</sub> component of the ibogaine-induced discriminative stimulus

AU Helsley, Scott; Fiorella, David; Rabin, R. A.; Winter, J. C.

CS Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY, 14214-3000, USA

SO Pharmacol., Biochem. Behav. (1998), 59(2), 419-425

CODEN: PBBHAU; ISSN: 0091-3057

PB Elsevier Science Inc.

DT Journal

LA English

AB In the present investigation, the ability of two known hallucinogens, lysergic acid dimethylamide (LSD) and (-)-2,5-dimethoxy-4-methyl-amphetamine (DOM), to substitute for the ibogaine-induced discriminative stimulus (10 mg/kg IP, 60 min pre-session) was assessed in Fischer-344 rats. In these subjects, intermediate levels of generalization were observed to both agents (LSD, 63%; DOM, 66.4%). This intermediate generalization was completely blocked by pretreatment with the 5-HT<sub>2A</sub> antagonist pirenpirone, suggesting that the ibogaine-like effects of these agents are mediated by the 5-HT<sub>2A</sub> receptor. However, pirenpirone did not antagonize ibogaine itself, nor did it antagonize the ibogaine-like effects of harmaline and 12-hydroxyibogamine (noribogaine). To further evaluate the serotonergic properties of ibogaine, in vivo protection assays and in vitro binding assays were employed. Micromolar 5-HT<sub>2A</sub> affinity was observed with ibogaine (92.5  $\mu$ M), 12-hydroxyibogamine (34.5  $\mu$ M), and harmaline (42.5  $\mu$ M). Despite the apparently low affinity of these agents, both ibogaine and harmaline, but not 12-hydroxyibogamine, produced significant protection from receptor alkylation by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) when given 60 min prior to this alkylating agent. The results of these studies suggest that although ibogaine may produce some of its effects via interactions with 5-HT<sub>2A</sub> receptors, these do not appear to be essential to the ibogaine-induced discriminative stimulus.

IT 481-88-9, 12-Hydroxyibogamine

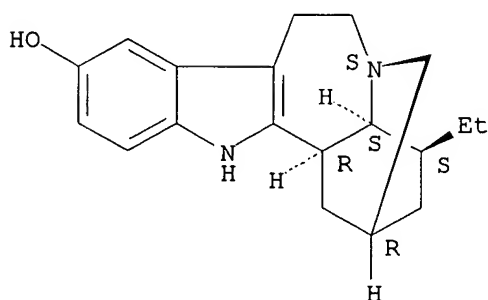
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)

(5-HT<sub>2A</sub> receptors role in mediating ibogaine and harmaline-induced discriminative stimulus)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1997:679297 CAPLUS

DN 128:266

TI Effects of noribogaine on the development of tolerance to antinociceptive action of morphine in mice

AU Bhargava, Hemendra N.; Cao, Ying-Jun

CS Department of Pharmaceutics and Pharmacodynamics (m/c 865), The University of Illinois at Chicago, Health Sciences Center, 833 South Wood Street, Chicago, IL, 60612, USA

SO Brain Res. (1997), 771(2), 343-346

CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier

DT Journal

LA English

AB The effects of noribogaine, a metabolite of ibogaine, on the development of tolerance to the antinociception action of morphine was detd. in male Swiss-Webster mice. Ibogaine is an alkaloid isolated from the bark of the African shrub, *Tabernanthe iboga*. Morphine tolerance in mice was developed by two different methods. Mice were rendered tolerant to morphine either by s.c. implantation of a pellet contg. 25 mg morphine free base for 4 days or by injecting morphine (20 mg/kg, s.c.) twice a day for 4 days. Placebo pellet implanted mice or vehicle injected mice served as controls. To det. the effect of i.p. administered noribogaine on tolerance development, the drug was injected in the appropriate dose twice a day. In pellet implanted mice, a dose of 20 mg/kg of noribogaine attenuated the tolerance to morphine whereas lower doses had no effect. Similarly, in mice given multiple injections of morphine, noribogaine attenuated tolerance development at 20 and 40 mg/kg doses. Previous studies from this lab. had shown that ibogaine at 40 and 80 mg/kg doses inhibited tolerance to morphine. Because noribogaine could attenuate morphine tolerance at lower doses than ibogaine, it is concluded that the attenuating effect of ibogaine on morphine tolerance may be mediated by its conversion to noribogaine, a more active metabolite.

IT 481-88-9, Noribogaine

RL: BAC (Biological activity or effector, except adverse); THU

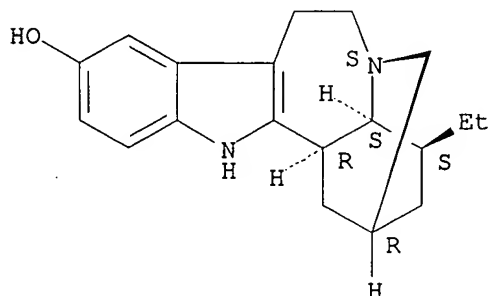
(Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of noribogaine on development of tolerance to antinociceptive action of morphine in mice)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1997:646580 CAPLUS

DN 127:341636

TI Time-dependent interactions between iboga agents and cocaine

AU Maisonneuve, Isabelle M.; Visker, Kathleen E.; Mann, Gina L.; Bandarage, Upul K.; Kuehne, Martin E.; Glick, Stanley D.

CS Department of Pharmacology and Neuroscience, A-136, Albany Medical College, 47 New Scotland Avenue, Albany, NY, 12208, USA

SO Eur. J. Pharmacol. (1997), 336(2/3), 123-126

CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier

DT Journal

LA English

AB The purpose of this study was to clarify the effects of iboga agents on cocaine-induced hyperactivity. Both inhibition and enhancement of cocaine-induced activity by ibogaine have been reported. In the present study, rats were treated with either ibogaine (40 mg/kg, i.p.), noribogaine (40 mg/kg, i.p.), 18-methoxycoronaridine (40 mg/kg, i.p.), or saline, 1 or 19 h prior to the administration of cocaine (20 mg/kg, i.p.) or saline. Motor activity was monitored thereafter for 3 h. All three iboga agents had acute inhibitory effects and delayed potentiating effects on cocaine-induced hyperactivity. These time-dependent effects, which could not be attributed to the motor activity induced by the iboga agents alone, account for divergent results reported in the literature.

IT 481-88-9, Noribogaine

RL: BAC (Biological activity or effector, except adverse); THU

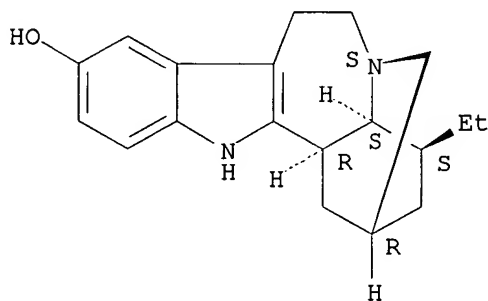
(Therapeutic use); BIOL (Biological study); USES (Uses)

(time-dependent interactions between iboga agents and cocaine-induced hyperactivity)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 21 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1997:521853 CAPLUS

DN 127:215026

TI Sex differences in ibogaine antagonism of morphine-induced locomotor activity and in ibogaine brain levels and metabolism

AU Pearl, S. M.; Hough, L. B.; Boyd, D. L.; Glick, S. D.

CS Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, 15260, USA

SO Pharmacol., Biochem. Behav. (1997), 57(4), 809-815

CODEN: PBBHAU; ISSN: 0091-3057

PB Elsevier

DT Journal

LA English

AB The present study demonstrates that the putative antiaddictive agent ibogaine produces more robust behavioral effects in female than in male rats and that these behavioral differences correlate with higher levels of ibogaine in the brain and plasma of female rats. There were no differences in basal locomotor activity between the sexes, and the response of rats to ibogaine differed between the sexes even in the absence of morphine. Five h after receiving ibogaine (40 mg/kg, IP), antagonism of morphine-induced locomotor activity was evident in female but not in male rats. Either 19 h after administration of ibogaine (10-60 mg/kg, IP), or one h after administration of noribogaine (5-40 mg/kg, IP), a suspected metabolite, antagonism of morphine was significantly greater in female than in male rats. Brain and plasma levels of ibogaine (1 h) and noribogaine (5 h), measured by gas chromatog.-mass spectrometry, were greater in females as compared with males receiving the same dose of ibogaine. Levels of both ibogaine and noribogaine were substantially lower at 19 h than at earlier times after ibogaine administration, contrary to a previous study in humans. For both sexes, s.c. administration of ibogaine (40 mg/kg, IP, 19 h) produced greater antagonism of morphine-induced locomotor activity than did a comparable i.p. injection, consistent with previous studies from this lab. demonstrating that the former route of administration produces higher levels of ibogaine in the brain. These data show that there are sex differences in the effects of ibogaine and that this may be due to decreased bioavailability of ibogaine in males as compared to females.

IT 481-88-9, Noribogaine

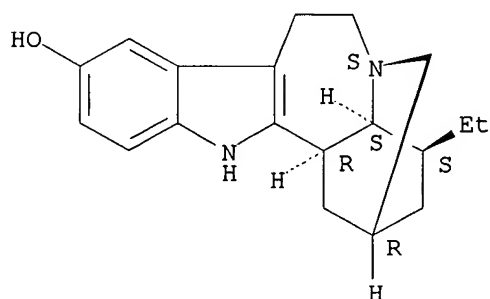
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(sex differences in ibogaine antagonism of morphine-induced locomotor activity and ibogaine brain levels and metab.)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

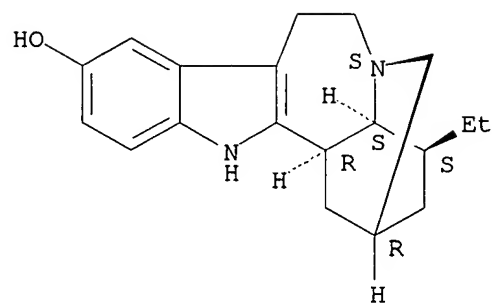




L25 ANSWER 22 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1997:156627 CAPLUS  
DN 126:246705  
TI Effects of ibogaine and noribogaine on the antinociceptive action of  
.mu.-, .delta.- and .kappa.-opioid receptor agonists in mice  
AU Bhargava, Hemendra N.; Cao, Ying-Jun; Zhao, Guo-Min  
CS Department of Pharmaceutics and Pharmacodynamics (M/C 865), The University  
of Illinois at Chicago, Health Sciences Center, 833 South Wood Street,  
Chicago, USA  
SO Brain Res. (1997), 752(1,2), 234-238  
CODEN: BRREAP; ISSN: 0006-8993  
PB Elsevier  
DT Journal  
LA English  
AB Ibogaine, an alkaloid isolated from the bark of the African shrub,  
Tabernanthe iboga, has been claimed to decrease the self-administration of  
drugs of abuse like morphine, cocaine and alc. To det. whether these  
effects are mediated via opioid receptor systems, the effects of ibogaine  
and its metabolite, noribogaine on the antinociceptive actions of  
morphine, U-50,488H and [D-Pen2,D-Pen5]enkephalin (DPDPE) which are .mu.-  
.kappa.- and .delta.-opioid receptor agonists, resp., were detd. in male  
Swiss-Webster mice. Administration of morphine (7 or 10 mg/kg, s.c.),  
U-50,488H (15 or 25 mg/kg, i.p.) or DPDPE (10 .mu.g/mouse, i.c.v.)  
produced antinociception in mice as measured by the tail-flick test.  
Ibogaine (10, 20 or 40 mg/kg, i.p.) by itself did not alter the tail-flick  
latency. The same doses of ibogaine injected 10 min before the opioid  
drugs did not modify the antinociceptive actions of morphine, U-50,488H or  
DPDPE. Ibogaine administered 4 h or 24 h prior to morphine injection did  
not modify the antinociceptive action of the latter. A dose of 40 mg/kg  
(i.p.) of noribogaine enhanced the antinociceptive activity of morphine  
(10 mg/kg, s.c.). Similarly, the doses of 40 and 80 mg/kg of noribogaine  
enhanced the antinociception produced by a smaller dose of morphine (5  
mg/kg, s.c.). However, antinociception induced by U-50,488H and DPDPE was  
not modified by noribogaine (10-40 mg/kg). It is concluded that ibogaine,  
which has been suggested to decrease the self-administration of cocaine  
and opiates like heroin in humans, does not produce such an action by  
interacting directly with multiple opioid receptors. However, the  
metabolite of ibogaine enhances the antinociception of morphine but not of  
U-50,488H or DPDPE. Thus, in vivo evidence has been provided for the  
possible interaction of ibogaine with .mu.-opioid receptor following its  
metab. to noribogaine.  
IT 481-88-9, Noribogaine  
RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(effects of ibogaine and noribogaine on antinociceptive action of  
opioid receptor agonists)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915



L25 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1997:102850 CAPLUS

DN 126:207400

TI The effects of noribogaine and harmaline in rats trained with ibogaine as a discriminative stimulus

AU Helsley, Scott; Rabin, Richard A.; Winter, J. C.

CS Dep. of Pharmacology and Toxicology, State University of New York at Buffalo, Buffalo, NY, 14214-3000, USA

SO Life Sci. (1997), 60(9), PL147-PL153

CODEN: LIFSAK; ISSN: 0024-3205

PB Elsevier

DT Journal

LA English

AB In the present investigation, Fischer-344 rats were trained to discriminate 10.0 mg/kg of ibogaine from water using a pretreatment time of 60 min. Anal. of dose response data generated an ED50 of 4.6 mg/kg. The time course of the ibogaine (10.0 mg/kg) cue was also detd. The stimulus reached a max. level of 94% ibogaine-appropriate responding at the 60-min pretreatment time. This was followed by a time-dependent decrease in ibogaine-appropriate responding. At a pretreatment time of 8 h only 6.4% drug-appropriate responding was obsd. In substitution expts., intermediate generalization was obsd. with a metabolite of ibogaine, 12-hydroxyibogamine [noribogaine] (71.6%) whereas complete generalization was seen with harmaline (83.5%).

IT 481-88-9, Noribogaine

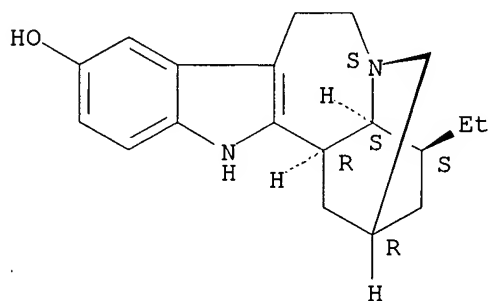
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(effects of noribogaine and harmaline in rats trained with ibogaine as discriminative stimulus)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1997:63998 CAPLUS

DN 126:233451

TI Ibogaine: a potent noncompetitive blocker of ganglionic/neuronal nicotinic receptors

AU Badio, Barbara; Padgett, William L.; Daly, John W.

CS Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 20892-0820, USA

SO Mol. Pharmacol. (1997), 51(1), 1-5

CODEN: MOPMA3; ISSN: 0026-895X

PB Williams &amp; Wilkins

DT Journal

LA English

AB Ibogaine noncompetitively blocked (IC<sub>50</sub> .apprx. 20 nM) <sup>22</sup>NaCl influx through ganglionic-type nicotinic receptor channels of rat pheochromocytoma PC12 cells. The major metabolite O-des-methylibogaine was 75-fold less active, and O-t-butyl-O-des-methylibogaine was 20-fold less active. Ibogaine was relatively weak as a blocker (IC<sub>50</sub> .apprx. 2000 nM) of the neuromuscular-type nicotinic receptor channels in human medulloblastoma TE671 cells. The blockade of nicotinic responses by ibogaine was only partially reversible in PC12 cells. In vivo, ibogaine at 10 mg/kg completely blocked epibatidine-elicited antinociception in mice, a response that is mediated by central nicotinic receptor channels. There was no significant blockade of the epibatidine response at 24 h after the administration of 40 mg/kg ibogaine. The blockade of nicotinic channels could contribute to the antiaddictive properties of ibogaine.

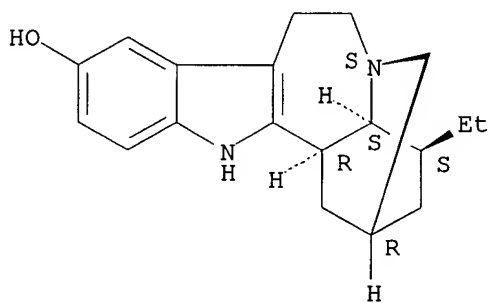
IT 481-88-9, O-Demethylibogaine

RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(ibogaine: a potent noncompetitive blocker of ganglionic/neuronal nicotinic receptors)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



10/075,915

L25 ANSWER 25 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1997:49269 CAPLUS

DN 126:152816

TI Method of treating chemical dependency using .beta.-carboline alkaloids, derivatives and salts thereof

IN Lotsof, Howard S.

PA NDA International, Inc., USA

SO U.S., 6 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5591738	A	19970107	US 1994-322490	19941014
OS	MARPAT 126:152816				

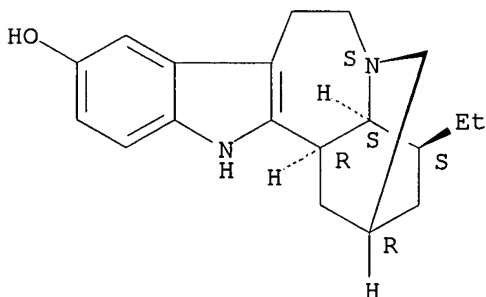
AB A method of treating a chem. dependency disorder, an abuse syndrome or a combination thereof in a mammal in need thereof, comprises administering (1) an effective amt. of a .beta.-carboline alkaloid, hydrolyzable deriv. or pharmaceutically-acceptable salt thereof, such as harmaline, harmine, tetrahydroharmine, tetrahydronorharman, harmol, harmalol, Et harmol, Pr harmol, iso-Pr harmol, and Bu harmol and (2) an effective amt. of a noribogaine compd.

IT 481-88-9, Noribogaine 176916-14-6, O-Benzoylnoribogaine  
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(chem. dependency treatment with .beta.-carboline alkaloids and noribogaine derivs.)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

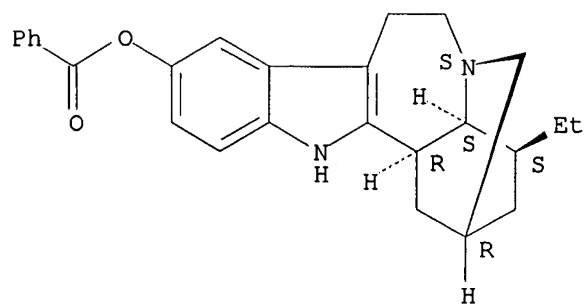


RN 176916-14-6 CAPLUS

CN Ibogamin-12-ol, benzoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/075,915



L25 ANSWER 26 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1996:726840 CAPLUS

DN 126:54741

TI Ibogaine and noribogaine potentiate the inhibition of adenylyl cyclase activity by opioid and 5-HT receptors

AU Rabin, Richard A.; Winter, Jerrold C.

CS Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY, 14214-3000, USA

SO Eur. J. Pharmacol. (1996), 316(2/3), 343-348

CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier

DT Journal

LA English

AB The effects of the putative anti-addictive compd. ibogaine and its principal metabolite, noribogaine, on adenylyl cyclase activity were detd. in various areas of the rat brain. Neither compd. altered either basal or forskolin-stimulated adenylyl cyclase activities in the frontal cortex, midbrain or striatum. However, in all three brain areas the addn. of ibogaine and noribogaine significantly enhanced inhibition of adenylyl cyclase activity by a maximally effective concn. of morphine. Similarly, both compds. also potentiated the inhibition of hippocampal adenylyl cyclase activity by a maximally effective concn. of 5-hydroxytryptamine (5-HT). Although ibogaine appears to be more potent than noribogaine in augmenting opioid- and 5-HT-mediated inhibition of adenylyl cyclase activity, both compds. appear to be of comparable efficacy. Neither compd., however, modified the inhibitory action of the muscarinic acetylcholine agonist, carbachol, on adenylyl cyclase activity. The present data indicate that ibogaine and noribogaine cause a selective increase in receptor-mediated inhibition of adenylyl cyclase activity. This potentiation may be involved in the pharmacol. actions of these compds.

IT 481-88-9, Noribogaine

RL: BAC (Biological activity or effector, except adverse); THU

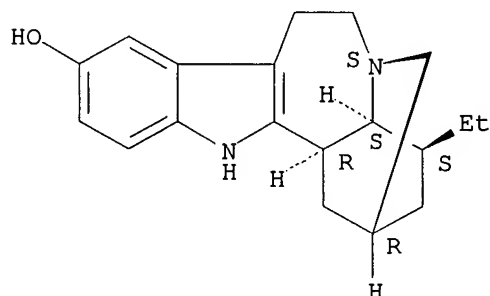
(Therapeutic use); BIOL (Biological study); USES (Uses)

(ibogaine and noribogaine potentiate inhibition of adenylyl cyclase activity by opioid and serotonin receptors)

RN 481-88-9 CAPLUS

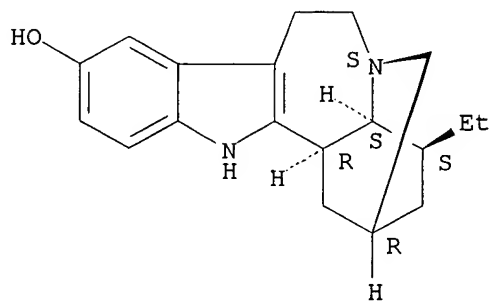
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1996:710970 CAPLUS  
DN 126:139743  
TI Facilitation of memory retrieval by the "anti-addictive" alkaloid,  
ibogaine  
AU Popik, Piotr  
CS Inst. Pharm., Polish Acad. Sci., Krakow, 31-343, Pol.  
SO Life Sci. (1996), 59(24), PL379-PL385  
CODEN: LIFSAK; ISSN: 0024-3205  
PB Elsevier  
DT Journal  
LA English  
AB Anecdotal observations in humans indicate that indole alkaloid ibogaine  
may have antiaddictive properties. It has been suggested that therapeutic  
action of ibogaine may depend upon facilitated access to the past  
experiences, purportedly influencing the initiation of drug addiction. To  
det. if ibogaine may facilitate memory retrieval, rats were trained in the  
Morris maze spatial navigation task. It has been found that ibogaine  
(0.25 or 2.5 mg/kg) or O-desmethyl-ibogaine, but not t-Bu ibogaine,  
administered just before the test trial, facilitated spatial memory  
retrieval compared to rats receiving placebo treatment. It is concluded  
that although previously described NMDA receptor antagonistic properties  
of ibogaine may represent a locus for at least some of its actions, other  
mechanisms, involving facilitation of memory retrieval may be of  
importance for its anti-addictive effects.  
IT **481-88-9, Ibogamin-12-ol**  
RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(facilitation of memory retrieval by the "anti-addictive" alkaloid,  
ibogaine)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

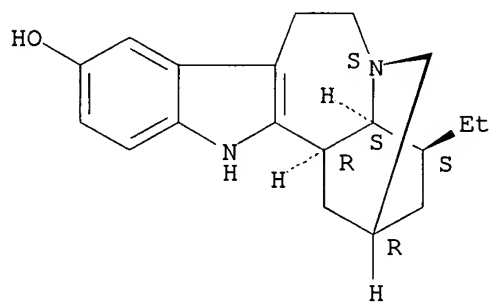
Absolute stereochemistry.





L25 ANSWER 28 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1996:692751 CAPLUS  
DN 126:26668  
TI Modulation of morphine-induced antinociception by ibogaine and noribogaine  
AU Bagal, A. A.; Hough, L. B.; Nalwalk, J. W.; Glick, S. D.  
CS Department of Pharmacology and Neuroscience, A-136, Albany Medical  
College, 47 New Scotland Ave., Albany, NY, 12208, USA  
SO Brain Res. (1996), 741(1,2), 258-262  
CODEN: BRREAP; ISSN: 0006-8993  
PB Elsevier  
DT Journal  
LA English  
AB The potential modulation of morphine antinociception by the putative  
anti-addictive agent ibogaine and its active metabolite (noribogaine) was  
investigated in rats with the radiant heat tail-flick test. Ibogaine  
pretreatment (40 mg/kg, i.p., 19 h) significantly decreased morphine (4  
mg/kg, s.c.) antinociception, with no effects in the absence of morphine.  
However, co-administration of ibogaine (1-40 mg/kg, i.p.) and morphine (4  
mg/kg, s.c.) exhibited a dose-dependent enhancement of morphine  
antinociception. Co-administration of noribogaine (40 mg/kg, i.p.) and  
morphine also resulted in an increase in morphine antinociception, while  
noribogaine pretreatment (19 h) had no effect on morphine antinociception.  
The results show that ibogaine acutely potentiates morphine  
antinociception and that noribogaine could be the active metabolite  
responsible for this effect. However, the inhibitory effects of a 19 h  
ibogaine pretreatment, which resemble ibogaine-induced inhibition of  
morphine's stimulant properties, cannot be accounted for by noribogaine.  
IT 481-88-9, Noribogaine  
RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(modulation of morphine-induced antinociception by ibogaine and  
noribogaine)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 29 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1996:572474 CAPLUS

DN 125:238572

TI Pharmacological screen for activities of 12-hydroxyibogamine: a primary metabolite of the indole alkaloid ibogaine

AU Staley, Julie K.; Ouyang, Qijie; Pablo, John; Hearn, W. Lee; Flynn, Donna D.; Rothman, Richard B.; Rice, Kenner C.; Mash, Deborah C.

CS Dep. Neurol., Univ. Miami Sch. Med., Miami, FL, 33101, USA

SO Psychopharmacology (Berlin) (1996), 127(1), 10-18

CODEN: PSCHDL; ISSN: 0033-3158

DT Journal

LA English

AB The purported efficacy of ibogaine for the treatment of drug dependence may be due in part to an active metabolite. Ibogaine undergoes first pass metab. and is O-demethylated to 12-hydroxyibogamine (12-OH ibogamine). Radioligand binding assays were conducted to identify the potency and selectivity profiles for ibogaine and 12-OH ibogamine. A comparison of 12-OH ibogamine to the primary mol. targets identified previously for ibogaine demonstrates that the metabolite has a binding profile that is similar, but not identical to the parent drug. Both ibogaine and 12-OH ibogamine demonstrated the highest potency values at the cocaine recognition site on the 5-HT transporter. The same rank order (12-OH ibogamine > ibogaine), but lower potencies were obsd. for the [3H]paroxetine binding sites on the 5-HT transporter. Ibogaine and 12-OH ibogamine were equipotent at vesicular monoamine and dopamine transporters. The metabolite demonstrated higher affinity at the kappa-1 receptor and lower affinity at the NMDA receptor complex compared to the parent drug. Quantitation of the regional brain levels of ibogaine and 12-OH ibogamine demonstrated micromolar concns. of both the parent drug and metabolite in rat brain. Drug dependence results from distinct, but inter-related neurochem. adaptations, which underlie tolerance, sensitization and withdrawal. Ibogaine's ability to alter drug-seeking behavior may be due to combined actions of the parent drug and metabolite at key pharmacol. targets that modulate the activity of drug reward circuits.

IT 481-88-9, 12-Hydroxyibogamine

RL: BAC (Biological activity or effector, except adverse); THU

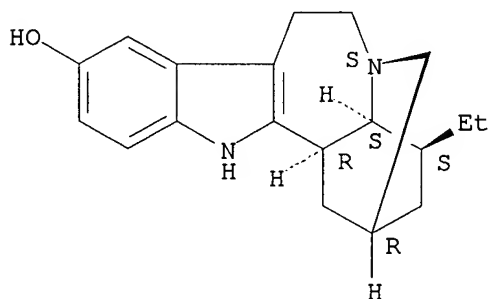
(Therapeutic use); BIOL (Biological study); USES (Uses)

(ibogaine metabolite 12-hydroxyibogamine in drug dependence treatment)

RN 481-88-9 CAPLUS

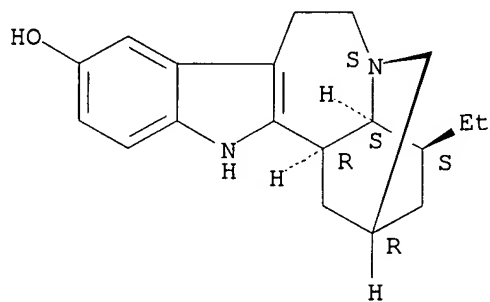
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1996:490818 CAPLUS  
DN 125:238257  
TI Effects of ibogaine and noribogaine on phosphoinositide hydrolysis  
AU Rabin, Richard A.; Winter, J. C.  
CS Department of Pharmacology and Toxicology, School of Medicine and  
Biomedical Sciences, State University of New York at Buffalo, 102 Farber  
Hall, Buffalo, NY, 14214-3000, USA  
SO Brain Res. (1996), 731(1,2), 226-229  
CODEN: BRREAP; ISSN: 0006-8993  
DT Journal  
LA English  
AB The effects of the antiaddictive compd., ibogaine, and its primary  
metabolite, noribogaine (12-hydroxyibogamine), on phosphoinositide  
hydrolysis were investigated. Although ibogaine did not alter  
phosphoinositide turnover in either striatal or hippocampal slices,  
noribogaine elicited a concn.-dependent increase in the generation of  
[3H]inositol phosphates. This stimulation was not altered by inclusion of  
tetrodotoxin, cadmium or .omega.-conotoxin indicating that the increased  
prodn. of [3H]inositol phosphates was not secondary to a release of one or  
more neurotransmitters. The present study indicates a stimulation of  
phosphoinositide hydrolysis by noribogaine may be involved in the  
behavioral effects of ibogaine.  
IT **481-88-9**, Noribogaine  
RL: BAC (Biological activity or effector, except adverse); BIOL  
(Biological study)  
(effects of ibogaine and noribogaine on phosphoinositide hydrolysis)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 31 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1996:475146 CAPLUS

DN 125:238250

TI Structurally modified ibogaine analogs exhibit differing affinities for NMDA receptors

AU Layer, Richard T.; Skolnick, Phil; Bertha, Craig M.; Bandarage, Upul K.; Kuehne, Martin E.; Popik, Piotr

CS Laboratory of Neuroscience, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

SO Eur. J. Pharmacol. (1996), 309(2), 159-165

CODEN: EJPHAZ; ISSN: 0014-2999

DT Journal

LA English

AB Based on both preclin. findings and anecdotal evidence in man, the psychoactive indole alkaloid ibogaine has been suggested to have anti-addictive properties. Previous studies indicate that blockade of NMDA receptors may mediate at least some of the putative anti-addictive actions of ibogaine. The potencies of a series of ibogaine analogs to inhibit (+)-[3-<sup>3</sup>H]5-methyl-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5,10-imine ([<sup>3</sup>H]MK-801) binding to NMDA receptors were examd. This series of analogs included the putative ibogaine metabolite O-desmethylibogaine, its metab.-resistant analog O-tert-Bu-O-desmethylibogaine, the iboga alkaloids (.+-.)-ibogamine, (.+-.)-coronaridine, tabernanthine, harmaline, and the indolotropanes endo-3-(1-methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (RS 075194-190), exo-3-(1-methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (RS 075237-190) and endo-3-(indol-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (RS 025989-190). Among these compds., ibogaine was the most potent inhibitor of [<sup>3</sup>H]MK-801 binding ( $K_i$  = .apprx.1.2 . $\mu$ M), while the compds. with the greatest structural similarity to ibogaine, O-desmethylibogaine and O-t-butyl-O-desmethylibogaine were less potent ( $K_i$  = .apprx.5.5 and 179.0 . $\mu$ M, resp.). In morphine-dependent mice, ibogaine, but not O-desmethylibogaine or O-t-butyl-O-desmethylibogaine, attenuated naloxone pptd. withdrawal jumping. These findings are consistent with the hypothesis that inhibition of the expression of morphine dependence by ibogaine is related to its NMDA receptor antagonist properties.

IT 481-88-9, Ibogamin-12-ol

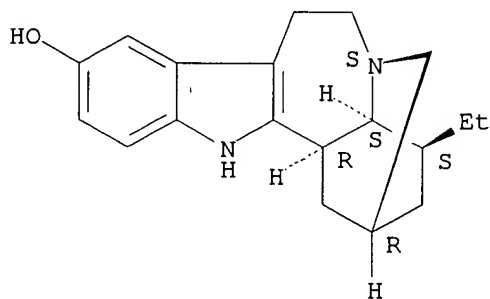
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(ibogaine analog affinity for NMDA receptor and drug dependence inhibition, and O-t-butyl-O-desmethylibogaine prepn.)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



10/075,915

L25 ANSWER 32 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1996:321083 CAPLUS

DN 124:333123

TI Noribogaine compounds for treating chemical dependency in mammals

IN Mash, Deborah C.; Sanchez-Ramos, Juan; Hearn, W. Lee

PA Nda International, Inc., USA

SO PCT Int. Appl., 19 pp.

CODEN: PIXXD2

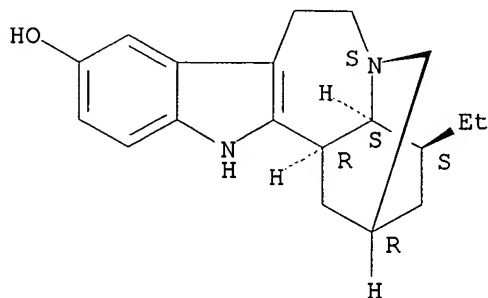
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 9603127	A1	19960208	WO 1995-US9136	19950725
	W: CA, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9646132	A1	19960419	AU 1996-46132	19950725
	EP 804200	A1	19971105	EP 1995-927295	19950725
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	US 6348456	B1	20020219	US 1996-727123	19961008
PRAI	US 1994-280187	A	19940725		
	WO 1995-US9136	W	19950725		
OS	MARPAT 124:333123				
AB	An essentially pure noribogaine compd., particularly noribogaine or a hydrolyzable deriv. thereof, reduces craving for addictive substances and is longer acting than ibogaine.				
IT	<b>481-88-9</b> , 12-Hydroxyibogamine <b>176916-13-5</b> , O-Acetylnoribogaine <b>176916-14-6</b> , O-Benzoylnoribogaine <b>176916-15-7</b> .				
	RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (noribogaine compds. for treating chem. dependency)				
RN	481-88-9 CAPLUS				
CN	Ibogamin-12-ol (9CI) (CA INDEX NAME)				

Absolute stereochemistry.

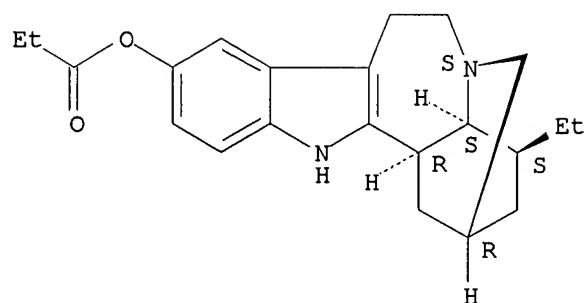


RN 176916-13-5 CAPLUS

CN Ibogamin-12-ol, propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

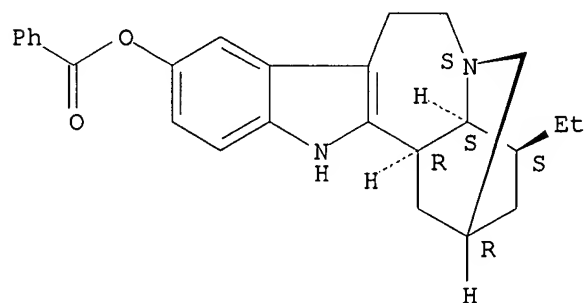
10/075,915



RN 176916-14-6 CAPLUS

CN Ibogamin-12-ol, benzoate (ester) (9CI) (CA INDEX NAME)

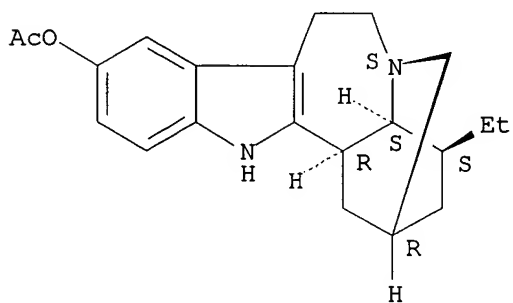
Absolute stereochemistry.



RN 176916-15-7 CAPLUS

CN Ibogamin-12-ol, acetate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1996:214023 CAPLUS

DN 124:279016

TI Ibogaine-like effects of noribogaine in rats

AU Glick, S. D.; Pearl, S. M.; Cai, J.; Maisonneuve, I. M.

CS Department of Pharmacology and Neuroscience, Albany Medical College, New Scotland Avenue, Albany, NY, 12208, USA

SO Brain Res. (1996), 713(1,2), 294-7

CODEN: BRREAP; ISSN: 0006-8993

DT Journal

LA English

AB Ibogaine is a naturally occurring alkaloid that has been claimed to be effective in treating addiction to opioids and stimulants; a single dose is claimed to be effective for 6 mo. Analogously, studies in rats have demonstrated prolonged (one or more days) effects of ibogaine on morphine and cocaine self-administration even though ibogaine is mostly eliminated from the body in several hours. These observations have suggested that a metabolite may mediate some of the effects of ibogaine. Recently, noribogaine was identified as a metabolite of ibogaine. Accordingly, the present study sought to det., in rats, whether noribogaine had pharmacol. effects mimicking those of ibogaine. Noribogaine (40 mg/kg) was found to decrease morphine and cocaine self-administration, reduce the locomotor stimulant effect of morphine, and decrease extracellular levels of dopamine in the nucleus accumbens and striatum. All of these effects were similar to effects previously obsd. with ibogaine (40 mg/kg); however, noribogaine did not induce any ibogaine-like tremors. The results suggest that noribogaine may be a mediator of ibogaine's putative anti-addictive effects.

IT 481-88-9, Noribogaine

RL: BAC (Biological activity or effector, except adverse); THU

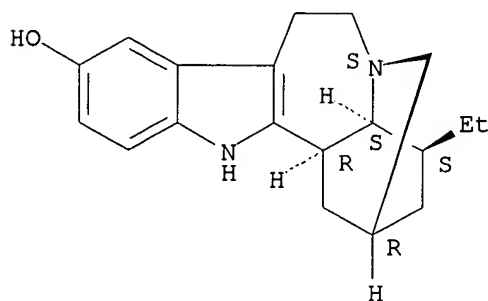
(Therapeutic use); BIOL (Biological study); USES (Uses)

(noribogaine decreases cocaine and morphine self-administration and extracellular levels of dopamine in brain)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 34 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1995:850984 CAPLUS

DN 123:275065

TI Identification and quantification of ibogaine and an o-demethylated metabolite in brain and biological fluids using gas chromatography-mass spectrometry

AU Hearn, William L.; Pablo, John; Hime, George W.; Mash, Deborah C.

CS Metro-Dade County Medical Examiner's Dep., Univ. of Miami School of Medicine, Miami, FL, 33136, USA

SO J. Anal. Toxicol. (1995), 19(6), 427-34

CODEN: JATOD3; ISSN: 0146-4760

DT Journal

LA English

AB This report describes a sensitive method for quantitating ibogaine and a single major metabolite in biol. fluids and brain tissue. We identified the metabolite as 12-hydroxy-ibogamine (12-OH-ibogamine or noribogaine) by full-scan, electron-impact gas chromatog.-mass spectrometry (GC-MS). Ibogaine, 12-OH-ibogamine, and o-(methyl)-ibogaine-d3 (ibogaine-d3) internal std. were isolated by solvent extn. under basic conditions. The resulting org. ext. was evapd. to dryness, and the residue was derivatized at room temp. with Et iodide in the presence of tri-Me anilinium hydroxide in DMSO. The reaction was terminated by acidification and washed with org. solvents to remove impurities. The aq. phase was then alkalized and reextd. The org. ext. was concd. and analyzed by GC-MS. Quantitation was based upon the ratios of the mol. ions at m/z 310 for ibogaine, m/z 313 for ibogaine-d3, and m/z 324 for 12-OH-ibogamine Et ether. The limit of detection was 5 ng/mL for both ibogaine and derivatized 12-OH-ibogamine, and limits of quantitation were between 5 and 10 ng/mL for all matrixes tested. Calibration curves were linear in the range of 5-1000 ng/mL or ng/g for both analytes.

IT 481-88-9, Noribogaine

RL: ANT (Analyte); MFM (Metabolic formation); ANST (Analytical study);

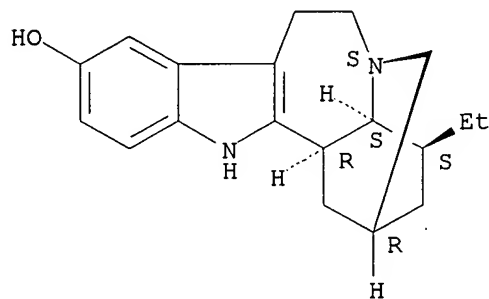
BIOL (Biological study); FORM (Formation, nonpreparative)

(ibogaine and noribogaine detn. in brain and biol. fluids by gas chromatog.-mass spectrometry)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.





L25 ANSWER 35 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1995:850978 CAPLUS

DN 123:275064

TI Determination of ibogaine and 12-hydroxy-ibogamine in plasma by gas chromatography-positive ion chemical ionization-mass spectrometry

AU Alburges, Mario E.; Foltz, Rodger L.; Moody, David E.

CS Center for Human Toxicology, Univ. of Utah, Salt Lake City, UT, 84112, USA

SO J. Anal. Toxicol. (1995), 19(6), 381-6

CODEN: JATOD3; ISSN: 0146-4760

DT Journal

LA English

AB Ibogaine, an indolamine deriv., is currently being investigated as a potential agent in the treatment of stimulant and opiate addiction. We developed a rapid, sensitive, and specific method for the anal. of ibogaine and its putative active metabolite, 12-hydroxy-ibogamine (12-OH-ibogamine). This assay employs a one-step basic extn. with Bu chloride-acetonitrile (4:1), followed by derivatization of the metabolite using N-methyl-N-(tert-butyldimethylsilyl)-trifluoroacetamide. The derivatized exts. were analyzed by capillary gas chromatog.-pos. ion chem. ionization-mass spectrometry. The ions monitored were at m/z 311, 314, and 411, which correspond to the protonated mols. (MH+) for ibogaine, ibogaine-d3, and 12-OH-ibogamine.cntdot.tert-butyldimethylsilyl, resp. Linear std. curves were obtained over the concn. range of 10-1000 ng/mL (av. r2, 0.995 for ibogaine and 0.992 for 12-OH-ibogamine; n = 3). Limits of quantitation were 10 ng/mL. The interrun and intrarun coeffs. of variation for the assay of ibogaine at 25, 100, and 300 ng/mL ranged from 2.9 to 8.8%. We also established the extn. and chromatog. conditions to monitor the 12-hydroxylated metabolite. A suitable internal std. was not yet obtained so the method could only provide semiquant. information for 12-OH-ibogamine. Chem. stability studies of these analytes indicated that ibogaine and 12-OH-ibogamine were stable in a human plasma matrix at room temp. for a period of at least 1 wk.

IT 481-88-9, 12-Hydroxy-ibogamine

RL: ANT (Analyte); MFM (Metabolic formation); ANST (Analytical study);

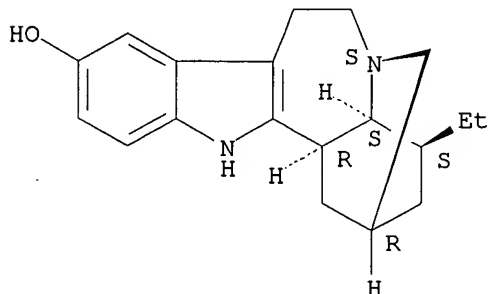
BIOL (Biological study); FORM (Formation, nonpreparative)

(ibogaine and hydroxyibogamine detn. in plasma by gas chromatog.-pos. ion chem. ionization-mass spectrometry)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 36 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1995:628238 CAPLUS

DN 123:74687

TI Properties of ibogaine and its principal metabolite (12-hydroxyibogamine) at the MK-801 binding site of the NMDA receptor complex

AU Mash, D. C.; Staley, J. K.; Pablo, J. P.; Holohean, A. M.; Hackman, J. C.; Davidoff, R. A.

CS Department of Neurology (D4-5), PO Box 016960, University of Miami School of Medicine, Miami, FL, 33101, USA

SO Neurosci. Lett. (1995), 192(1), 53-6

CODEN: NELED5; ISSN: 0304-3940

DT Journal

LA English

AB The putative anti-addiction alkaloid ibogaine and its principal metabolite 12-hydroxyibogamine appear to act at the (+)-5 methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-10-imine maleate (MK-801) binding site in the N-methyl-D-aspartate (NMDA)-receptor cation channel. This conclusion is based on findings that both compds. competitively displaced specific [3H]MK-801 binding to membranes from postmortem human caudate and cerebellum and from frog spinal cord. Ibogaine was 4-6-fold more potent than its metabolite and both compds. were less potent (50-1000-fold) than MK-801 binding to the NMDA receptor. In addn., ibogaine (100 .mu.M) and 12-hydroxyibogamine (1 mM) blocked (85-90% of control) the ability of NMDA (100 .mu.M, 5 s) to depolarize frog motoneurons in the isolated frog spinal cord. The prevention of NMDA-depolarizations in frog motoneurons showed use-dependency and was very similar to the block produced by MK-801. In view of the abilities of MK-801 to affect the responses to addictive substances in pre-clin. investigations, our results are compatible with the idea that the ability of ibogaine and 12-hydroxyibogamine to interrupt drug-seeking behavior may, in part, result from their actions at the MK-801 binding site.

IT 481-88-9, Ibogamin-12-ol

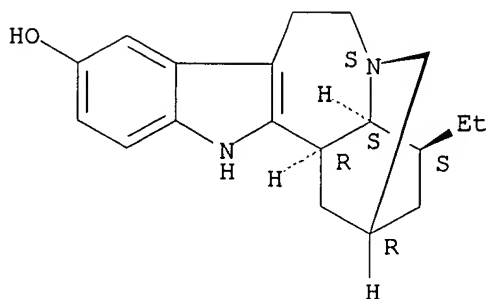
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(prevention of drug-seeking by ibogaine and hydroxyibogamine and role of MK-801 binding site of the NMDA receptor complex)

RN 481-88-9 CAPLUS

CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2002 ACS

AN 1995:621179 CAPLUS

DN 123:47718

TI Identification of a primary metabolite of ibogaine that targets serotonin transporters and elevates serotonin

AU Mash, Deborah C.; Staley, Julie K.; Baumann, Michael H.; Rothman, Richard B.; Hearn, W. Lee

CS Dep. Neurology, Univ. Miami School Medicine, Miami, FL, 33136, USA

SO Life Sci. (1995), 57(3), PL45-PL50

CODEN: LIFSAK; ISSN: 0024-3205

DT Journal

LA English

AB Ibogaine is a hallucinogenic indole with putative efficacy for the treatment of cocaine, stimulant and opiate abuse. The purported efficacy of ibogaine following single dose administrations has led to the suggestion that a long-acting metabolite of ibogaine may explain in part how the drug reduces craving for psychostimulants and opiates. We report here that 12-hydroxyibogamine, a primary metabolite of ibogaine, displays high affinity for the 5-HT transporter and elevates extracellular 5-HT. In radioligand binding assays, 12-hydroxyibogamine was 50-fold more potent at displacing radioligand binding at the 5-HT transporter than at the DA transporter. Ibogaine and 12-hydroxyibogamine were equipotent at the dopamine transporter. In vivo microdialysis was used to evaluate the acute actions of ibogaine and 12-hydroxyibogamine on the levels of DA and 5-HT. Administration of 12-hydroxyibogamine produced a marked dose-related elevation of extracellular 5-HT. Ibogaine and 12-hydroxyibogamine failed to elevate DA levels in the nucleus accumbens over the dose range tested. The elevation in synaptic levels of 5-HT by 12-hydroxyibogamine may heighten mood and attenuate drug craving. The effects of the active metabolite on 5-HT transmission may account in part for the potential of ibogaine to interrupt drug-seeking behavior in humans.

IT 481-88-9, 12-Hydroxyibogamine

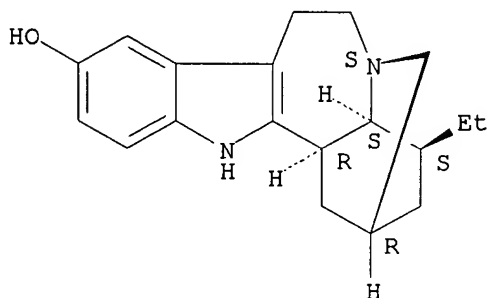
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)

(hydroxyibogamine as ibogaine metabolite that targets serotonin transporters and elevates serotonin)

RN 481-88-9 CAPLUS

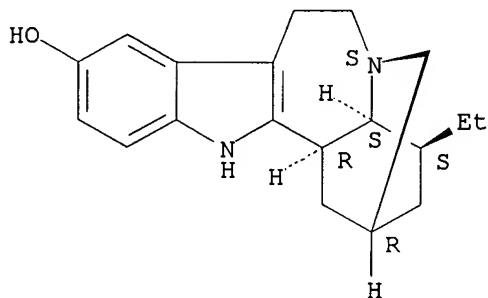
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



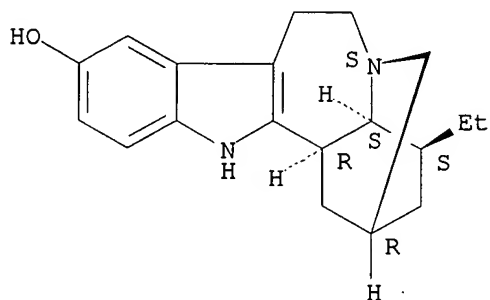
L25 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1995:608544 CAPLUS  
DN 123:74811  
TI Ibogaine and its congeners are .sigma.2 receptor-selective ligands with moderate affinity  
AU Bowen, Wayne D.; Vilner, Bertold J.; Williams, Wanda; Bertha, Craig M.; Kuehne, Martin E.; Jacobson, Arthur E.  
CS Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 20892, USA  
SO Eur. J. Pharmacol. (1995), 279(1), R1-R3  
CODEN: EJPHAZ; ISSN: 0014-2999  
DT Journal  
LA English  
AB Ibogaine (12-methoxyibogamine) exhibited moderate affinity for .sigma.2 sites ( $K_i = 201$  nM) and low affinity for .sigma.1 sites ( $K_i = 8554$  nM), thus showing 43-fold selectivity for .sigma.2 receptors. Tabernanthine (13-methoxyibogamine) and (.+-.)-ibogamine had .sigma.2  $K_i = 194$  nM and 137 nM, resp. However, they showed 3- to 5-fold higher .sigma.1 affinity compared to ibogaine, resulting in about 14-fold selectivity for .sigma.2 sites over .sigma.1. A potential ibogaine metabolite, O-des-methyl-ibogaine, had markedly reduced .sigma.2 affinity relative to ibogaine ( $K_i = 5,226$  nM) and also lacked significant affinity for .sigma.1 sites. (.+-.)-Coronaridine ((.+-.)-18-carbomethoxyibogamine) and harmaline (1-methyl-7-methoxy-3,4-dihydro-.beta.-carboline) lacked significant affinity for either .sigma. subtype. Thus, .sigma.2 receptors could play a role in the actions of ibogaine.  
IT **481-88-9**, Ibogamin-12-ol  
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(ibogaine and its congeners are .sigma.2 receptor-selective ligands with moderate affinity)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 39 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1995:448716 CAPLUS  
DN 122:256172  
TI Radioligand-binding study of noribogaine, a likely metabolite of ibogaine  
AU Pearl, Sandra M.; Herrick-Davis, Katherine; Teitler, Milton; Glick, Stanley D.  
CS Department of Pharmacology and Neuroscience, A-136, Albany Medical College, 47 New Scotland Avenue, Albany, NY, 12208, USA  
SO Brain Res. (1995), 675(1,2), 342-4  
CODEN: BRREAP; ISSN: 0006-8993  
DT Journal  
LA English  
AB Radioligand-binding studies were performed to ascertain the actions of noribogaine, a suspected metabolite of ibogaine, on opioid receptors in calf brain cortex and caudate. Consistent with previous results, ibogaine showed highest affinity for .kappa. opioid receptors ( $K_i = 3.77 \mu\text{M}$ ), less affinity for .mu. receptors ( $K_i = 11.04 \mu\text{M}$ ) and no affinity for .delta. receptors ( $K_i > 100 \mu\text{M}$ ). Noribogaine showed a higher affinity than ibogaine for all of the opioid receptors: .kappa.  $K_i = 0.96 \mu\text{M}$ , .mu.  $K_i = 2.66 \mu\text{M}$  and .delta.  $K_i = 24.72 \mu\text{M}$ . These data suggest that noribogaine is active in vivo and that it may contribute to ibogaine's pharmacol. effects.  
IT **481-88-9**, Ibogamin-12-ol  
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(binding of noribogaine and ibogaine to brain opioid receptor subtypes)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 40 OF 40 CAPLUS COPYRIGHT 2002 ACS  
AN 1972:522079 CAPLUS  
DN 77:122079  
TI Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids  
AU Zetler, G.; Singbartl, G.; Schlosser, Lucie  
CS Inst. Pharmakol., Med. Akad. Luebeck, Luebeck, Ger.  
SO Pharmacology (1972), 7(4), 237-48  
CODEN: PHMGBN  
DT Journal  
LA English  
AB With the exception of harmalol-HCl, which was effective only when injected intracerebrally, all the other 8 alkaloids tested produced tremor in mice when given s.c. The 4 most active compds. and their ED50 values were tabernanthine (I) [83-94-3] (1.4 mg/kg), ibogaline [482-18-8] (2.6 mg/kg), harmaline [304-21-2] (3.2 mg/kg), and harmine-HCl [17018-99-4] (3.9 mg/kg). Kinetics of evasion from brain were first-order functions with most drugs, but revealed for harmalol and ibogaline 2 and 3 compartments, resp. Tremor-producing activity was much more influenced by chem. structure than by lipid soly.  
IT **481-88-9**  
RL: BIOL (Biological study)  
(tremor from, metabolism by brain in relation to)  
RN 481-88-9 CAPLUS  
CN Ibogamin-12-ol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

